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HLA DRB1*DQB1* Haplotype in HTLV-I-Associated Familial Infective Dermatitis May Predict Development of HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis

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A possible causal association between infective dermatitis and HTLV-I infection was reported in 1990 and confirmed in 1992. We now report familial infective dermatitis (ID) occurring in a 26-year-old mother and her 9-year-old son. The mother was first diagnosed with ID in 1969 at the age of 2 years in the Dermatology Unit at the University Hospital of the West Indies (U.H.W.I.) in Jamaica. The elder of her 2 sons was diagnosed with ID at the age of 3 years, also at U.H.W.I. Both mother and son are HTLV-I-seropositive. A second, younger son, currently age 2 years, is also HTLV-I-seropositive, but without clinical evidence of ID. Major histocompatibility complex (MHC), class II, human leucocyte antigen (HLA) genotyping documented a shared class II haplotype, DRB1*DQB1* (1101-0301), in the mother and her 2 sons. This same haplotype has been described among Japanese patients with HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and has been associated with a possible pathologically heightened immune response to HTLV-I infection. The presence of this haplotype in these familial ID cases with clinical signs of HAM/TSP may have contributed to their risk for development of HAM/TSP. The unaffected, HTLV-I-seropositive, younger son requires close clinical follow-up.

KEY WORDS: HLA, DRB1, DQB1, HTLV-I, infective dermatitis, HTLV-I-associated myelopathy, tropical spastic paraparesis, Jamaica

INTRODUCTION

Infective dermatitis of Jamaican children was first described as a distinct clinical entity by Sweet [1966] and Walshe [1967]. The main manifestations are exudative dermatitis with crusting affecting the scalp, neck, axillae, and groin, a generalized fine papular rash, a watery nasal discharge and/or crusting of the anterior nares, culture of staphylococcus aureus (SA) and/or β-hemolytic streptococcus (BHS) from the anterior nares or skin of the patients, and the need for long-term antibiotic therapy for control of the dermatitis. Walshe [1967] postulated that these children might be immunosuppressed, hence their inability to effectively overcome infection with the bacteria, SA and BHS, and the resulting need for long-term antibiotics.

Human T-lymphotropic virus type I (HTLV-I) was the first human retrovirus to be identified [Poiesz et al., 1980]. It was first found to be causally associated with adult T-cell leukemia/lymphoma (ATL) [Takatsuki et al., 1977], and later with HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [Gessain et al., 1985]. In 1990, the association between infective dermatitis of Jamaican children and HTLV-I infection was reported [LaGrenade et al., 1990]. This association was subsequently confirmed in an analysis where clinical and laboratory findings of 50 patients with infective dermatitis were contrasted with a comparison group of 36 atopic eczema patients [LaGrenade et al., 1992]. In this report, the data suggested that HTLV-I infection might be the cause of the immune dysfunction among

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ID patients. Although most carriers remain asymptomatic, HTLV-I infection is nevertheless well documented as causing immune system alterations [Popovic et al., 1984; Kronke et al., 1985; Tachibana et al., 1988; Neva et al., 1989].

The first case of infective dermatitis evolving into ATL after 17 years was reported by Hanchard et al. [1991], and the occurrence of HAM/TSP in 2 patients with ID developing after 12 and 25 years has also been observed [LaGrenade et al., 1994]. We now report the familial occurrence of infective dermatitis in a mother and her son.

CLINICAL REPORTS

Patient 1

S.M., a 26-year-old woman, was seen in the dermatology clinic of the University Hospital of the West Indies (U.H.W.I.) at age 1 year and 10 months, with a 5-month history of severe intermittent rashes and frequent "colds." There was no past medical or family history at that time of skin disease or of atopy. On examination, she was found to have watery nasal discharge, generalized fine papular rash, and an exudative eczema with crusting of her face, scalp, and neck. There were no obvious signs of malnutrition and no significant lymphadenopathy.

A clinical diagnosis of infective dermatitis was supported by cultures of SA from her skin and from nasal swabs. Her hemoglobin (Hb) was 9.9 g/dl with mild hypochromia, and the white blood cell (wbc) count was 9.1×10^9/l with a differential of 50% lymphocytes and 44% neutrophils. She was treated with oral antibiotics and a mixture of topical steroids and topical antibiotics to the skin lesions. She responded well and was discharged after 6 weeks on oral antibiotics and topical steroids.

She was followed as an outpatient and remained fairly well for the next 5 years until, at age 7, she was noted to be developing corneal opacities. She was treated in the ophthalmology clinic of the U.H.W.I. with topical antibiotics and vitamin A supplements; the corneal opacities improved somewhat but were still present 2 years later.

She continued to attend the dermatology clinic regularly and remained relatively well until age 11 years, when she ran out of medication and had another exacerbation of her dermatitis. She was readmitted for 2 weeks, and once again a swab from her nostrils was cultured and grew both SA and BHS. *Trichuris trichiura* was found on stool microscopy, Hb was 12.g/dl, and wbc count was 7.5×10^9/l. She has continued to attend the dermatology clinic since then, defaulting for short periods only, and has required no further hospital admissions.

When the patient presented for a follow-up visit in 1994, she reported symptoms of frequency and urgency of micturition of 2 years' duration. On neurologic examination she had early but definite evidence of HAM/TSP, supported by findings of hyperreflexia in all limbs with predominance in the lower limbs, bilateral clonus, and extensor plantar responses. Superficial and deep sensation were intact, and gait was normal.

Her prior history was also remarkable for the birth of her first son, D.W., when she was age 17 years, and a second pregnancy, at age 20 years, which produced a second son who was delivered at home but died 5 days later. Another son was born when she was 24 years old.

Patient 2

D.W., son of S.M. (patient 1), presented to the dermatology clinic at U.H.W.I. at age 3 years with a 1-year history of a skin rash similar to that of his mother. She had treated him with some of her own medication, which had helped initially, but she brought him to the clinic because the rash had worsened and he had developed a purulent discharge from both eyes. On examination, he was found to have a severe blepharoconjunctivitis and findings typical of infective dermatitis. He was admitted to the dermatology ward where he was managed jointly with the ophthalmology service. Investigations on admission showed a heavy growth of SA and BHS on swab from the eyes, Hb of 9.6 g/dl, and wbc count of 13×10^9/l with 75% lymphocytes and 16% neutrophils.

He was treated with systemic and topical antibiotics and topical steroids. He responded well and was discharged after 2 weeks. Since then, he has continued to attend the clinic with his mother and has remained well, requiring no further admissions.

On a follow-up visit to clinic in 1994, he was examined neurologically and had evidence of hyperreflexia in all limbs; knee jerks were clonic, plantar responses were flexor, and only the right upper abdominal reflex was elicited. There were no other signs or symptoms, but the abnormal reflexes were suggestive of possible early damage to the pyramidal tracts in the spinal cord.

Since HTLV-I antibody testing became available in 1989, mother and son were tested, and both were seropositive for IgG antibodies to HTLV-I, with Western blot confirmation. HIV-1 antibody testing was negative in both patients. Skin biopsies in both showed subacute dermatitis.

MATERIALS AND METHODS

The parents and sibs of the 2 patients (S.M. and D.W.) were contacted, and consent was obtained for a clinical examination, in particular of the skin, lymphatic system, and nervous system. Blood samples were collected for HTLV-I antibody testing and a complete blood count. Western blot confirmation was sought if antibodies to HTLV-I were found. Selected HTLV-I-seropositive samples were titered using a particle agglutination (PA) assay. Human leukocyte antigen (HLA) serological typing for major histocompatibility complex (MHC), class I (A, B, C locus) and class II (DR, DQ locus), was performed using the standard microcytotoxicity test [Terasaki et al., 1978]. In addition, class II loci genotyping was performed and haplotypes were determined following DNA extraction [Maniatis et al., 1989], with DRB1 and DQB1 alleles identified by the SMI-Test (Sumitomo Metal Industries, Bio-Medical Division, Sagamihara, Japan) for HLA. This method is based on the PCR-RFLP method combined with group-specific primers [Ota et al., 1992].

RESULTS

HTLV-I antibody results on relatives are summarized in Figure 1. For simplification, 12 spouses/partners who fathered children were omitted from the pedigree in generation II, since no clinical data or HTLV-I serology results were available. Frequently, multiple partners resulted in producing offspring within each family unit. However, transmission of HTLV-I appeared to be accounted for by mother-to-child infection. On clinical examination, only the 2 affected cases (II-8, III-18) were found to have a skin rash. No relatives examined had any evidence of neurological disorders, including HAM/TSP. Complete blood counts were normal in all relatives, and there was no evidence of ATL. Among 30 other relatives tested, 7 (23%) were positive for HTLV-I antibodies, but only S.M. (II-8) and her son D.W. (III-18) had ID.

HLA haplotype results of the index case (II-8) and her offspring are presented in Table I. Each living offspring inherited the same haplotype, A29Cw4B7 DRB1*DQB1*(1101-0301), from the mother, but different haplotypes from the father. Each child had a different father. The paternal haplotype inherited in the infective dermatitis case (III-18) was A3Cw4B35 DRB1*DQB1*(0101-0501), while the younger offspring (III-20) inherited A26Cw1B55 DRB1*DQB1* (0102-0501). The HTLV-I antibody titer was higher in the 2 infective dermatitis cases (both >1/8192 vs. 1/256) than in the unaffected HTLV-I-seropositive offspring, suggesting that the disease state results in or is preceded by an enhanced antibody response.

In order to identify whether a particular haplotype was associated with ID and/or HTLV-I infection, several other relatives were typed as shown in Table I. HTLV-I-seropositive sibs of the index case (II-6, II-7) did not share haplotypes with the index case; however, they shared the same genotype with each other. HTLV-I antibody titers among these sibs were low compared to the 2 ID cases.

DISCUSSION

Walshe [1967], in her case-control study of infective dermatitis, postulated that immunosuppression played a part in the pathogenesis of this disease. In our study [LaGrenade et al., 1992], which confirmed the association between HTLV-I infection and infective dermatitis, the data demonstrated evidence of altered immune function with hyperactivity of both the humoral and cellular immune systems, though the precise immunological abnormality remains to be elucidated. However, the question has remained: why do some children infected with HTLV-I (a minority) develop infective dermatitis, while most remain asymptomatic [Pate et al., 1989]? This suggests the role of other factors in the development of infective dermatitis, and two possibilities are: 1) environment or lifestyle related to socioeconomic status [Murphy et al., 1991], since the patients are usually from the lower socioeconomic sections of the population; and 2) the immunogenetic background, as postulated here.

The occurrence of HTLV-I-associated infective dermatitis in this mother and son gave us a unique opportunity to test whether genetic susceptibility plays a role in this disease. Study of this family has been informative in many ways.

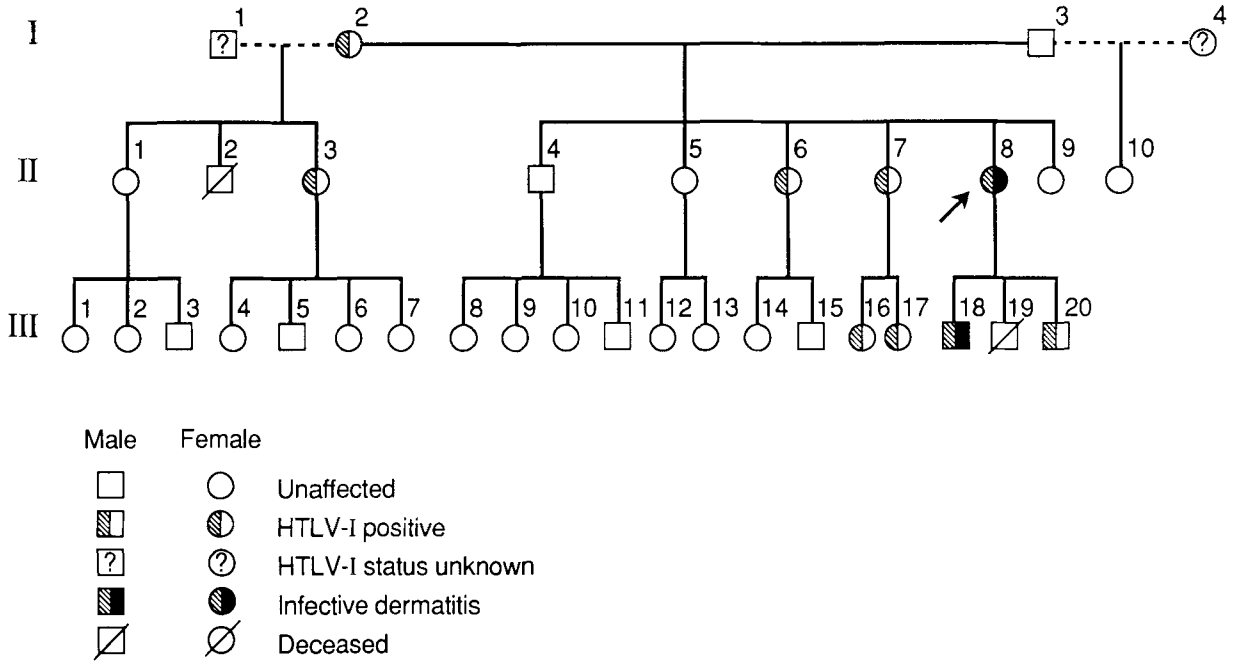

Fig. 1. Pedigree distribution of relatives with HTLV-I serostatus. Arrow indicates index case. Roman numerals (I–III) identify successive generations.

TABLE I. HLA Typing for Family Members*

ID	Age/sex	Relation	HLA serotypes A	C	B	Bw4/6	DR-DQ alleles DR	DRB1*	DQB1*	HTLV-I PA antibody titers
II-6	31/F	Sister	A2/A23	Cw6/–	B53/–	Bw4/Bw6	DR2/DR3	1602/0302	0502/0402	1/64
II-7	28/F	Sister	A2/A23	Cw6/–	B53/–	Bw4/Bw6	DR2/DR3	1602/0302	0502/0402	1/2,048
II-8	26/F	Index	A26/A29	Cw4/–	B7/B35	Bw6/–	DR11/DR13	1101/1301	0301/0501	>1/8,192
III-18	9/M	Son	A3/A29	Cw4/–	B7/B35	Bw6/–	DR11/DR1	1101/0101	0301/0501	>1/8,192
III-20	2/M	Son	A26/A29	Cw1/Cw4	B7/B35	Bw6/–	DR11/DR1	1101/0102	0301/0501	1/256

*ID, subject identification in pedigree, Figure 1; F, female; M, male; PA, particle agglutination test.

First of all, the structure of the household deserves comment, as it is representative of many households of a similar socioeconomic status in Jamaica. The grandmother and grandfather shown in the pedigree were originally small farmers; both had children outside the union before coming together and establishing a stable household and a marriage producing 6 children. All children, both of the union and before the union, now live in the same household with their own children and grandchildren of the original couple. Thus, there are three generations of the extended family living in the same household. This means that there is close physical contact between all relatives, but there has been no horizontal transmission of HTLV-I infection: only children of infected mothers have acquired infection. This supports the theory that the main route of infection for infective dermatitis is from mother to child.

Genetic studies of this family involved HLA typing for MHC, class I and class II loci, for the index case, her 2 sons, and 2 of her 6 sibs who shared the same mother and father. Results indicate that the mother and her 2 sons are the only relatives to share a common haplotype. This lends support to a possible genetic predisposition contributing to the development of ID. The absence of ID in the younger son (III-20) may be related to the fact that he is only 2 years old, which is the mean age of onset for ID [Carberry et al., 1992]; or, conversely, the different allele inherited from the unaffected child's father may be protective against disease. Close clinical follow-up is warranted. We also observed that the mother and son with ID had very high HTLV-I antibody titers, far greater than those of the other HTLV-I-seropositive sibs. No specific haplotype could be associated with the presence of HTLV-I infection among relatives.

The DRB1*DQB1*(1101-0301) haplotype present in the mother and her 2 sons is also one of the two haplotypes associated with HAM/TSP among Japanese patients [Usuku et al., 1988], which correlates with a high immune response and high antibody titers to HTLV-I. The mother had clinical evidence of HAM/TSP, and the son (III-18) with ID had early signs of possible neurologic dysfunction. Further identification in the son (III-18) of a second haplotype, DRB1*DQB1*(0101-0501), associated with Japanese HAM/TSP patients, possibly contributes to the predisposition for HAM/TSP. Usuku et al. [1988] have suggested that the HLA haplotype DRB1*DQB1* may determine susceptibility to development of ATL and HAM/TSP. It also seems plausible that this haplotype may determine susceptibility to infective dermatitis, although definitive conclusions should not be based on evaluation of this single family. However, we find further support for this hypothesis in the fact that we have already reported on 2 patients with infective dermatitis who developed HAM/TSP after 12 and 25 years, respectively [LaGrenade et al., 1994], and 1 patient who developed ATL after 17 years [Hanchard et al., 1991].

To further define these relationships, a family study of infective dermatitis, HAM/TSP, and ATL, already underway, will facilitate our insights into genetic susceptibility factors in these disease conditions.

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